Pentalfa, March 5th, 2020

UZ LEUVEN

KU LEUVEN

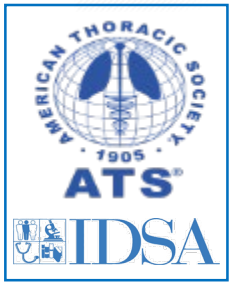


Management of respiratory infections

community-acquired pneumonia

Jan Verbakel, KU Leuven
Pascal Van Bleyenbergh, UZ Leuven





AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay*, Grant W. Waterer*, Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I. Restrepo, and Cynthia G. Whitney; on behalf of the American Thoracic Society and Infectious Diseases Society of America

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY MAY 2019 AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA AUGUST 2019



Pneumonia (community-acquired): antimicrobial prescribing

NICE National Institute for Health and Care Excellence



Severity of pneumonia

In adults, severity is assessed by clinical judgement guided by mortality risk score (CRB65 or CURB65):

- low severity - CRB65 score 0 or CURB65 score 0 or 1
- moderate severity - CRB65 score 1 or 2 or CURB65 score 2
- high severity - CRB65 score 3 or 4 or CURB65 score 3 to 5

In children and young people, severity is assessed by clinical judgement.

Prescribing considerations

When choosing an antibiotic(s), take account of:

- the severity assessment (adults), or the severity of symptoms or signs (children and young people); see above
- the risk of complications, for example, a relevant comorbidity (such as severe lung disease or immunosuppression)
- local antimicrobial resistance and surveillance data (such as flu and *Mycoplasma pneumoniae* infection rates)
- recent antibiotic use
- previous microbiological results, including colonisation with multi-drug resistant bacteria

Give oral antibiotics first line if possible

Review intravenous antibiotics by 48 hours and consider switching to oral antibiotics if possible

September 2019

Pneumonia (community-acquired)

H

Refer adults to hospital in line with NICE's guideline on pneumonia or if:

- symptoms or signs suggest a more serious illness such as sepsis, or
- symptoms are not improving as expected with antibiotics

Consider referring adults or seeking specialist advice if they have bacteria resistant to oral antibiotics or they cannot take oral medicines

Consider referring children and young people to hospital or seek specialist paediatric advice on further investigation and management

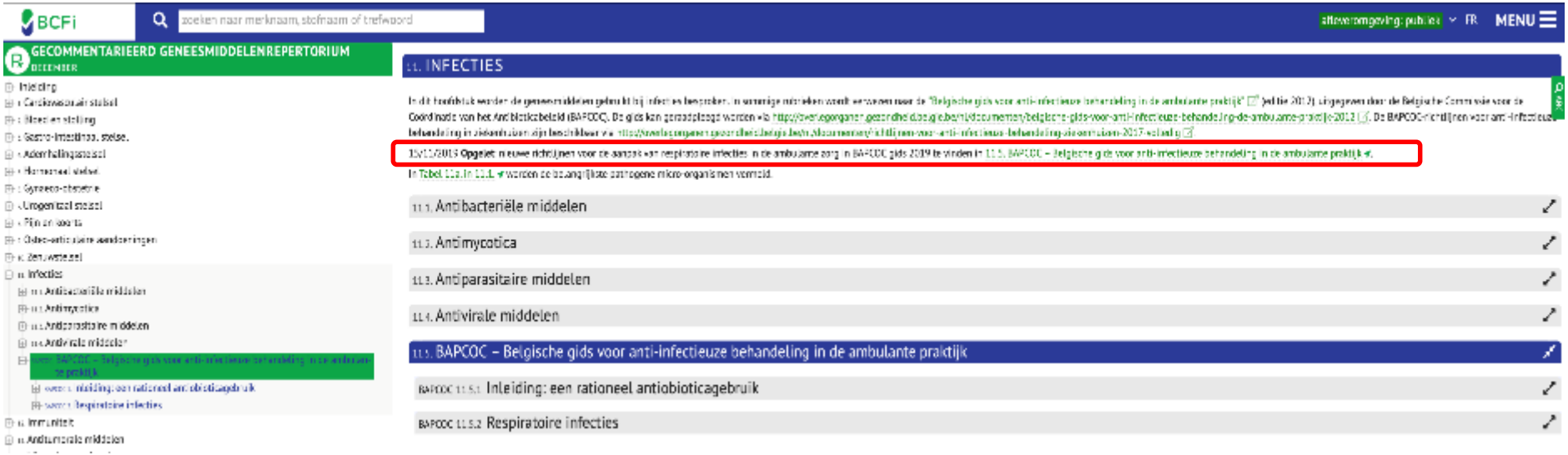


NICE guidance, 2019: https://www.nice.org.uk/guidance/ng138

VOLKSGEZONDHEID, VEILIGHEID VAN DE VOEDSELKETEN EN LEEFMILIEU

Belgische commissie voor de coördinatie van het antibioticabeleid (BAPCOC)

(http://overlegorganen.gezondheid.belgie.be/nl/advies-en-overlegorgaan/commissies/BAPCOC)









DOCUMENTEN

Categorie: Infecties van de onderste | Trefwoord: Een woord intikken ... | Tags: | ZOEKEN

Tags: lijst van reeds geselecteerde trefwoorden waaruit kan gekozen worden.
Trefwoorden: door de beheerder vrij in te vullen trefwoord.
Er wordt enkel naar het trefwoord of de tag gezocht in de door de bezoeker geselecteerde categorie (door geen categorie te selecteren kunnen alle documenten doorzocht worden).

Document (Op de titel klikken om het document te openen)	Categorie
Parapneumonische effusie, thoracaal empyeem; vroegtijdige, nosocomiale infectie bij pasgeborenen, zuigelingen, kinderen.	Infecties van de onderste luchtwegen.
Parapneumonische effusie, thoracaal empyeem: laattijdige, nosocomiale infectie bij pasgeborenen, zuigelingen, kinderen.	Infecties van de onderste luchtwegen.
Pertussis (kinkhoest).	Infecties van de onderste luchtwegen.
Pertussis (kinkhoest) (bijzondere patiëntengroepen).	Infecties van de onderste luchtwegen.
Pneumonie bij immuuncompetente adolescenten en/of volwassenen: community acquired infectie (CAP), voorafgaandelijke opmerkingen.	Infecties van de onderste luchtwegen.
Pneumonie bij immuuncompetente adolescenten en/of volwassenen: community acquired infectie (CAP), subgroep I.	Infecties van de onderste luchtwegen.
Pneumonie bij immuuncompetente adolescenten en/of volwassenen: community acquired infectie (CAP), subgroep II.	Infecties van de onderste luchtwegen.
Pneumonie bij immuuncompetente adolescenten en/of volwassenen: community acquired infectie (CAP), subgroep III.	Infecties van de onderste luchtwegen.
Pneumonie bij immuuncompetente adolescenten en/of volwassenen: community acquired infectie (CAP), subgroep IV.	Infecties van de onderste luchtwegen.





PNEUMONIE BIJ IMMUUNCOMPETENTE ADOLESCENTEN EN VOLWASSENEN: COMMUNITY ACQUIRED INFECTIE (CAP), VOORAFGAANDELIJKE OPMERKINGEN

- ***Aanbevelingen***
  - De aanbevelingen in deze gids maken gebruik van de CAP subgroep classificatie (subgroepen I, II, III en IV) gebaseerd op een aantal geïdentificeerde risicofactoren voor mortaliteit en gecompliceerd verloop.
  - Verder werd ook rekening gehouden met de Belgische epidemiologie.

- ***Diagnose***
  - Een rx thorax is nodig ter bevestiging van de diagnose, ook bij ambulante patiënten.
  - Het is onmogelijk, enkel en alleen op basis van de klinische tekens en symptomen, zekerheid te verwerven omtrent de betrokken pathogeen (hoogstens kan een gok worden gewaagd).
  - Diagnostische methodes [*Diagn Microbiol Infect Dis 2016;86:102*, *Clin Infect Dis 2016;62:817*, *Clin Chest Med 2017;38:21*, *Clin Infect Dis 2011;52(suppl. 4):S296*, *Scand J Infect Dis 2008;40:131*, *Clin Infect Dis 2010;50:202*, *Med Mal Infect 2011;41(suppl. 1):H2*] voor de identificatie van de pathogenen [staal: bloed, sputum, endotracheaal aspiraat, stalen bekomen via invasieve procedures (BAL), urine].
    - Ambulante patiënten (CAP subgroepen I en II): gramkleuring, bacteriële cultuur en opzoeken van biomarkers voor de identificatie van bepaalde pathogenen zijn niet noodzakelijk.
    - Gehospitaliseerde patiënten (CAP subgroepen III en IV).
      - 2 bloedstalen voor hemocultuur (*J Paediatr Child Health 2017;53:232*, *Hosp Pediatr 2015;5:324*).
      - Sputumevaluatie.
        - Gramkleuring en cultuur indien purulent sputum beschikbaar is en tijdig kan verwerkt worden. De predominante aanwezigheid van een bepaald morfologisch type van bacteriën bij een gramkleuring laat toe bepaalde gevolgen te trekken omtrent de etiologie.
        - Cultuur voor identificatie en gevoeligheidsbepalingen.
      - Opsporen van *Streptococcus pneumoniae* antigen in de urine is aangewezen bij patiënten die worden gehospitaliseerd omwille van de ernst van de pneumonie [*Respirology 2014;19:936*, *Clin Infect Dis 2003,36:286*, *Eur Respir J 2003;21:209*, *J Clin Microbiol 2013;51:2303*, *J Microbiol Methods 2016;121:24*, *Clin Microbiol Infect 2011;17(suppl. 3):1*]. Het uitvoeren van deze test moet ook worden overwogen wanneer pleuravocht wordt afgenomen in de context van een parapneumonische effusie. De test mag niet worden gebruikt bij kinderen omwille van de lage specificiteit (dragerschap van *Streptococcus pneumoniae*).
        Kwantitatieve moleculaire testen voor de detectie van *Streptococcus pneumoniae*, zowel in sputum als in bloed, kunnen waardevol zijn bij CAP patiënten bij wie de behandeling reeds is gestart (*Scand J Infect Dis 2013;45:731*, *J Clin Microbiol 2014;52:83*, *Infect Chemother 2013;45:351*). Zij kunnen ook een nuttig middel zijn om de ernst van de infectie in te schatten.
      - Opsporen van *Legionella* spp. antigen in de urine (uitstekende gevoeligheid en specificiteit) is aangewezen bij patiënten die worden gehospitaliseerd omwille van de ernst van de pneumo-

Casus: 78 jaar oud



- *Bekend met diabetes mellitus en arteriële hypertensie*
  Medicatie: Metformine, langwerkend insuline en hydrochloorthiazide

- *Hoest sinds vier weken, met geel sputum.*
  Afgelopen week drie dagen koorts gehad, nu niet meer
- *KO: geen dyspnee, O_2 sat 91%, longen wat verspreide rhonchi*

- *<u>Vraag</u>:*
  Verdere diagnostiek? Verder beleid?

Lower respiratory tract infections (LRTI)

- Respiratory tract infections are most common reason for primary care consultations

  ➜ ≥30% are LRTI

- Pneumonia: 5% - 10% of patients with LRTI symptoms and signs

- Bacterial and viral etiology clinically indistinguishable

- LRTI major reason for antibiotic presciption

Macfarlane J et al. *Thorax* 2001; 56: 109-114
Creer DD et al. *Thorax* 2006; 61: 75-79

Voor welke indicaties worden AB geschreven?

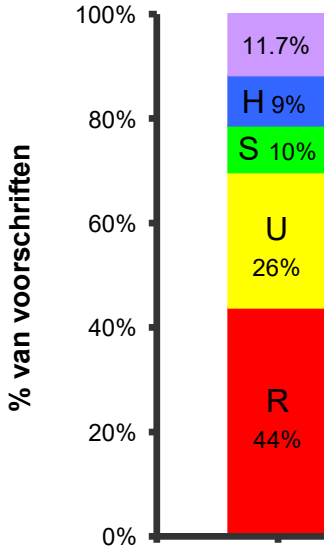
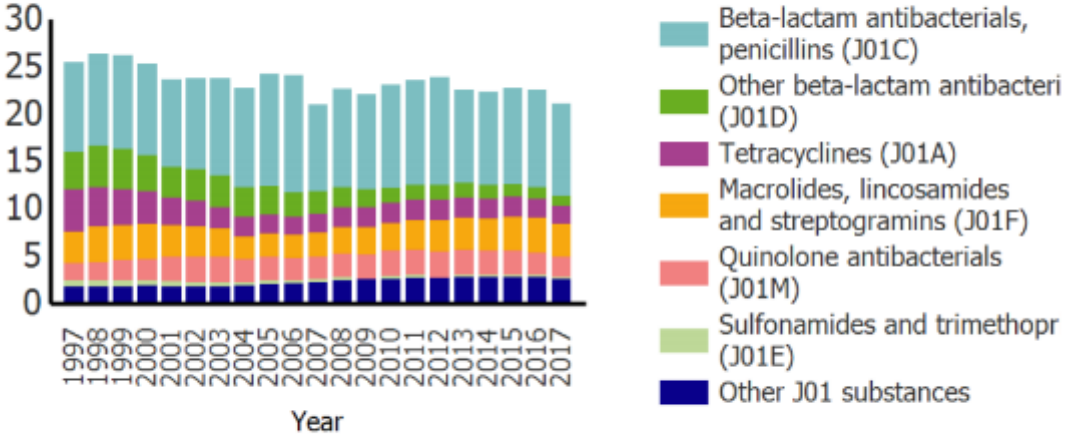


Figure 9 – Trend in the use of antibiotics for systemic use (ATC group J01) in the Belgian ambulatory sector expressed as DDD per 1000 inhabitants per day, 1997-2017



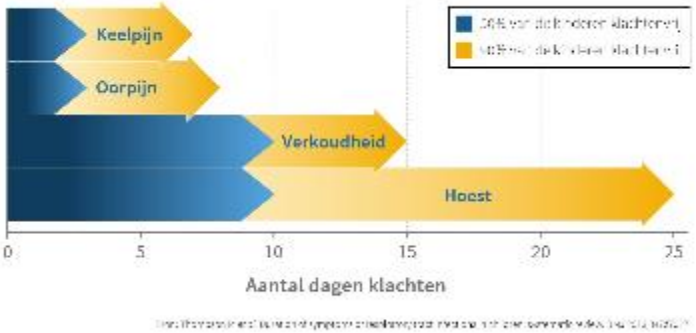
Source: European Centre for Disease Prevention and Control, ESAC-Net interactive website, 2019[109]

Effectiviteit antibiotica: etiologie

Gunstig natuurlijk beloop

Viraal / bacterieel

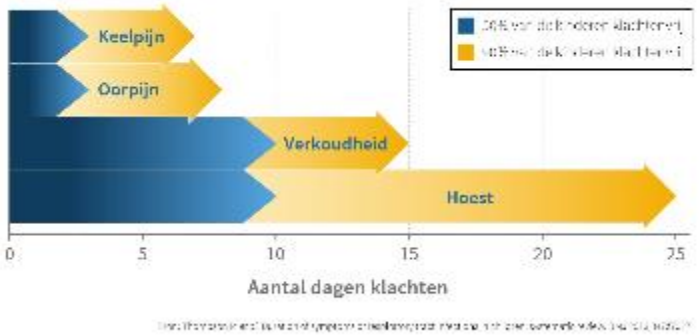
- OMA:
  - 40% geen bacteriële verwekker
  - Strep pneumoniae, Haemophilus influenzae
- Sinusitis:
  - vaak viraal
  - 1/3 van pat bij HA: Strep pneumoniae, Haemophilus influenzae
- Keelontsteking:
  - vaak viraal
  - 9-55% bacterieel (betahemolytische streptokok, vnl A)



Effectiviteit antibiotica: etiologie

Gunstig natuurlijk beloop

Viraal / bacterieel



- Hoest/bronchitis:
  - 40-60%: geen verwekker aangetoond
  - >1/2: viraal (influenza A, rhinovirus)
  - <1/2: bacterieel (Strep/M pneumoniae, Haemophilus influenzae)
- Pneumonie:
  - volwassenen: bacterieel > viraal
  - kinderen: vaker viraal (RSV, (para) influenza, adeno)

Interventies tegen overmatig AB gebruik

- UK (Francis, Butler)

Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial

controle	CRP	communicatie	CRP + com
53%	31%	27%	23%

- Nederland (Cals)

Effect of point of care testing for C-reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial

- Nederland – scholing, feedback (Velden/Verheij)

Improving antibiotic prescribing quality: intervention embe

practice accreditation

	AB	controle
A/CA/CE	-8%	+0.1%
CR/FA	-13%	+3%
over-prescriptie	44 → 28%	
onder-prescriptie	3 → 1%	

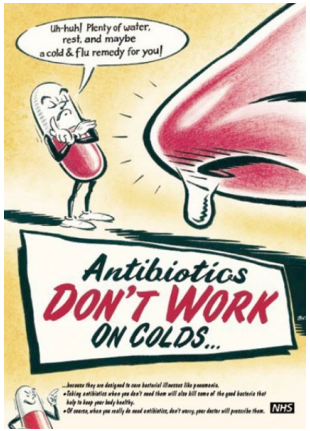
GO VIRAL

- Europa - internet training (Little)

Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial.



Campagnes tegen overmatig AB gebruik

















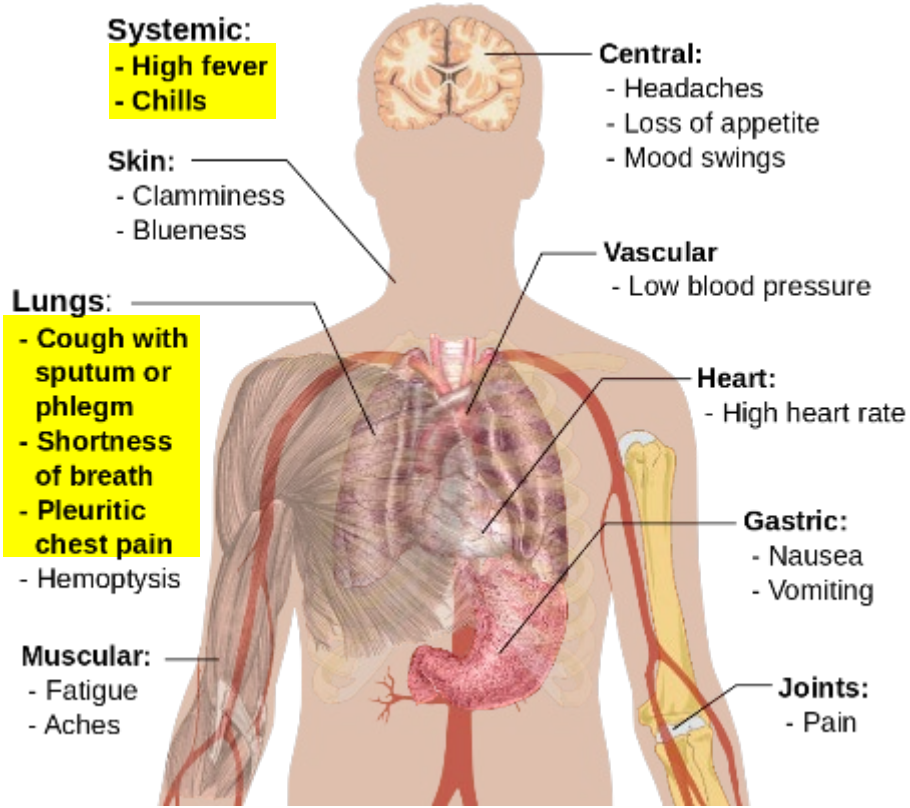








LRTI / CAP: symptoms & signs



Does This Patient Have Community-Acquired Pneumonia?

Diagnosing Pneumonia by History and Physical Examination

JAMA®
The Journal of the American Medical Association

- Individual **symptoms & signs have inadequate test characteristics to rule in or rule out the diagnosis** of pneumonia.

- Often disagreement about the presence or absence of individual findings on chest examination

- ‘Decision rules’ are not accurate enough

- If **diagnostic certainty** is required ⇨ **chest x-ray** necessary!



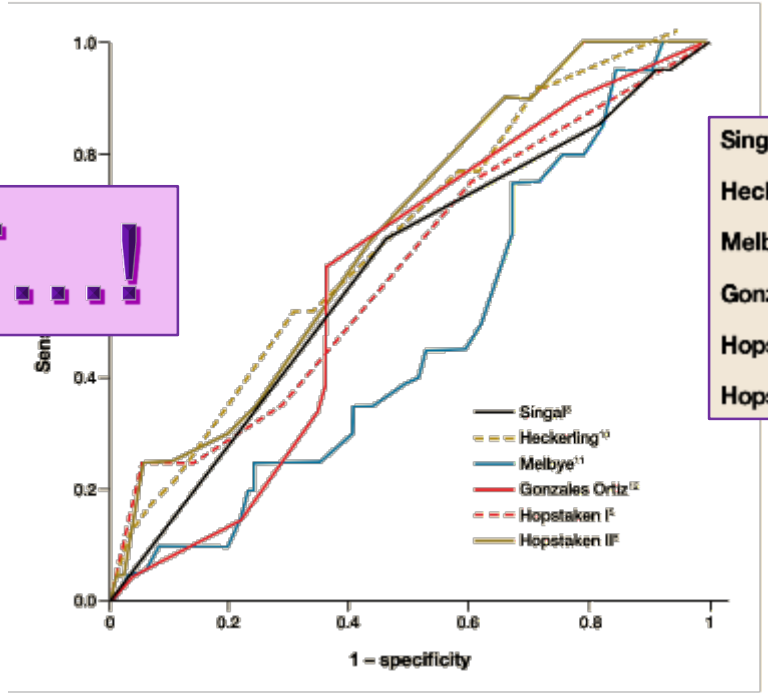
Metlay JP et al. *JAMA* 1997; 278(7): 1440-1445

Can history and exam alone reliably predict pneumonia?

THE JOURNAL OF FAMILY PRACTICE

Singal[8]	Y = −3.539 − 0.691 for cough − 0.681 for fever − 0.464 for crackles − 0.030 for 20.18 [illegible]
Heckerling[10]	Y = −1.76 0.494 for temperature >37.[illegible] − 0.428 for pulse >100 beats/[illegible]
González Ortiz[12]	Y = −1.87 1.3 for asthmatic auscultation − 1.84 for neutrophils 1.70 for pleural pain − 1.21 for dyspnea
Hopstaken I[5]	Y = −2.74 − 1.02 for dry cough − 1.78 for diarrhea − 1.13 for temperature >38°C
Hopstaken II[5]	Y = −4.15 − 0.81 for dry cough 1.01 for diarrhea − 0.64 for temperature >38°C − 2.76 for C-reactive protein ≥20 mg/L

NO, IT CAN'T...!



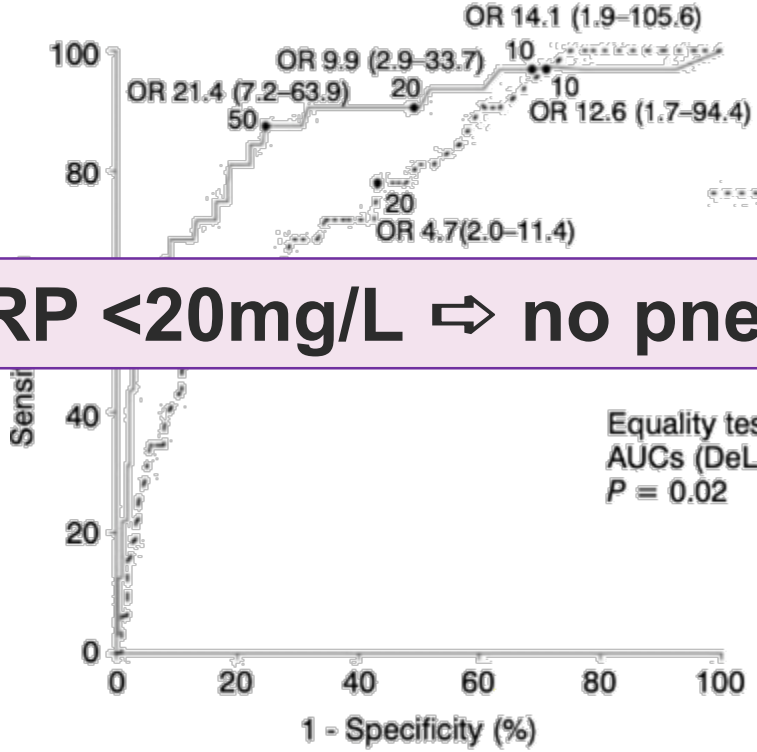
Singal[8]	0.58 (0.45–0.70)
Heckerling[10]	0.63 (0.50–0.75)
Melbye[11]	0.49 (0.37–0.62)†
González Ortiz[12]	0.57 (0.45–0.68)
Hopstaken I[5]	0.62 (0.50–0.75)
Hopstaken II[5]	0.69 (0.58–0.80)‡

Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection









CRP <20mg/L ⇨ no pneumonia

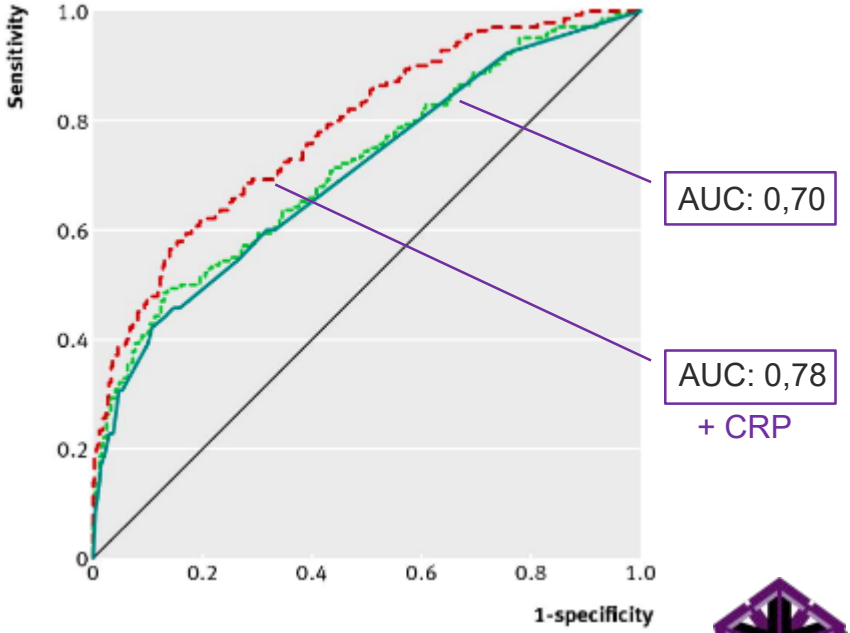
Hopstaken RM et al. *Br J Gen Pract* 2003; 53: 358-364

Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study

Saskia F van Vugt *general practitioner* [1], Berna D L Broekhuizen *assistant professor* [1], Christine Lammens *analyst* [2], Nicolaas P A Zuithoff *assistant professor* [1], Pim A de Jong *radiologist* [3], Samuel Coenen *assistant professor* [2], Margareta Ieven *professor* [2], Chris C Butler *professor* [4], Herman Goossens *professor* [2], Paul Little *professor* [5], Theo J M Verheij *professor* [1], on behalf of the GRACE consortium

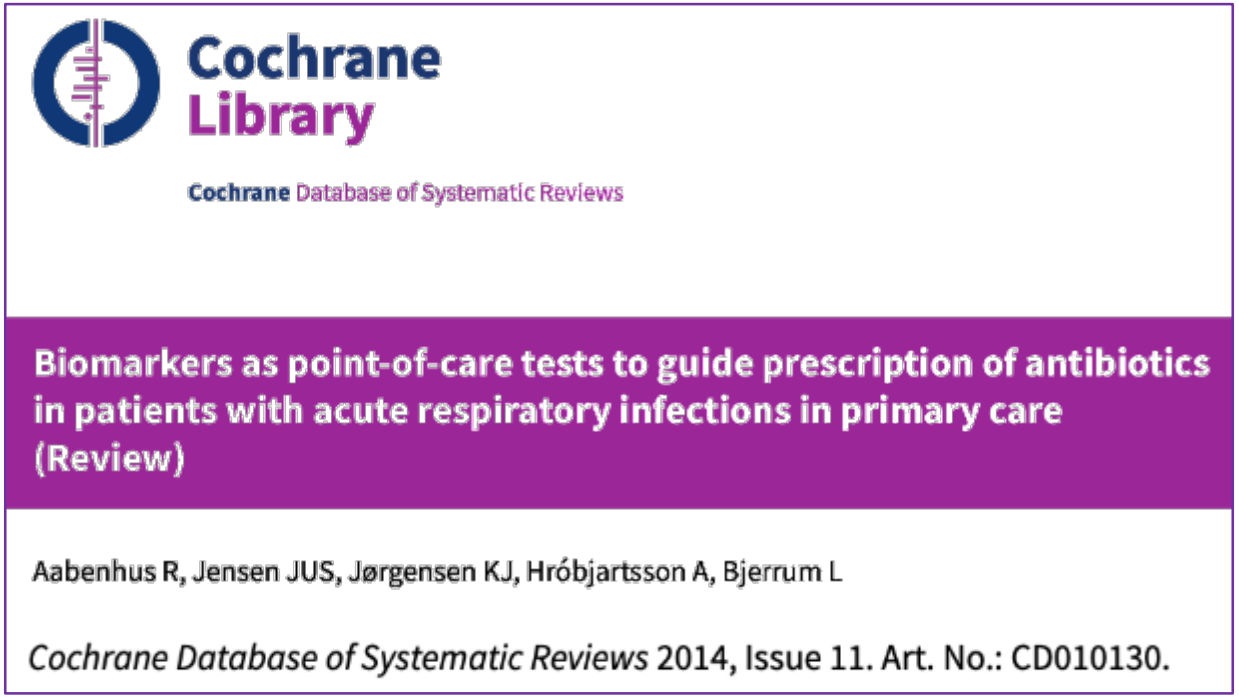
Signs & symptoms

- no runny nose
- breathlessness
- crackles and diminished breath sounds on auscultation
- tachycardia (>100/min)
- fever (temperature ≥37.8°C)

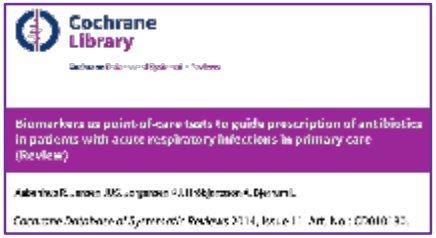


Van Vugt SF et al. *BMJ* 2013; 346: f2450

Biomarkers in CAP



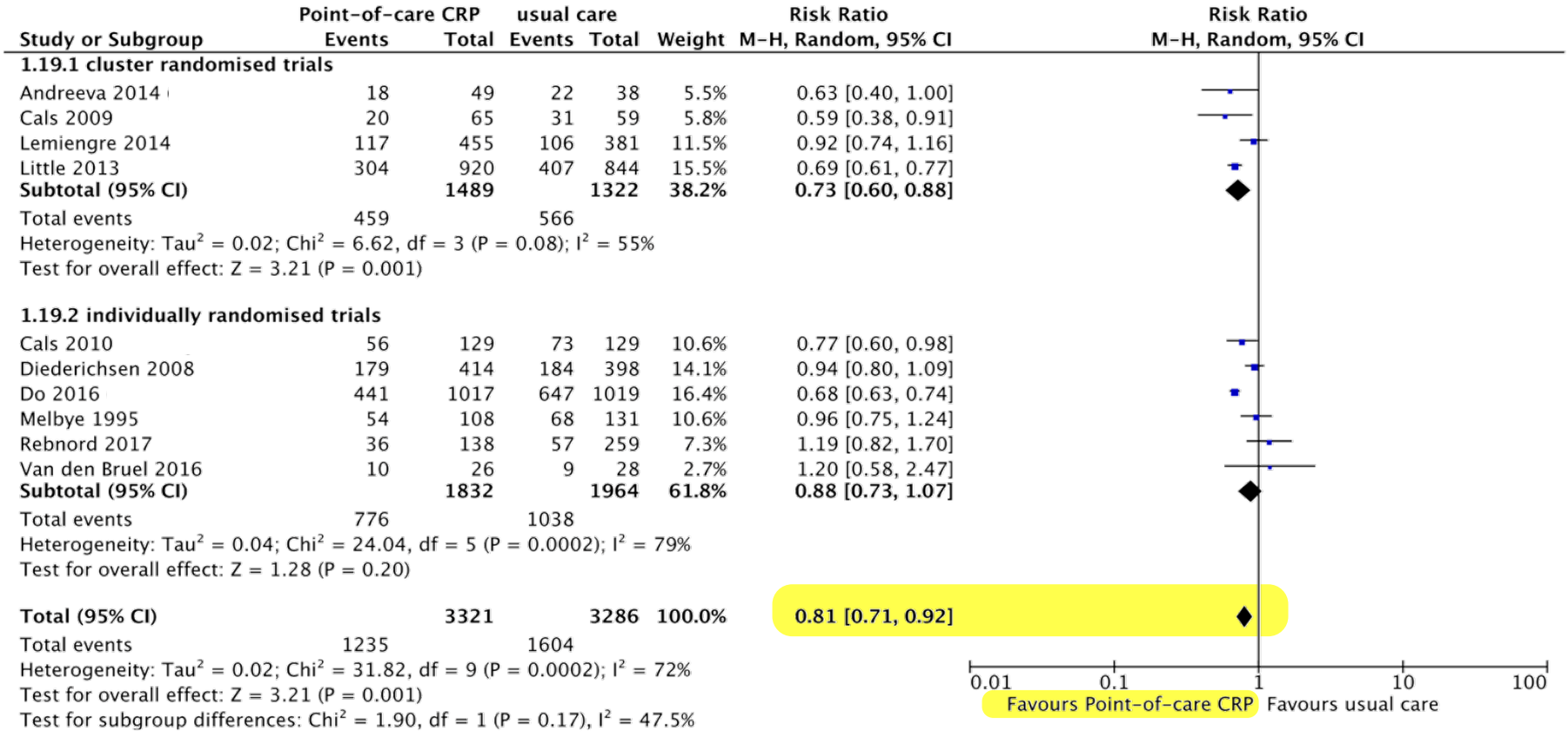
Biomarkers in CAP

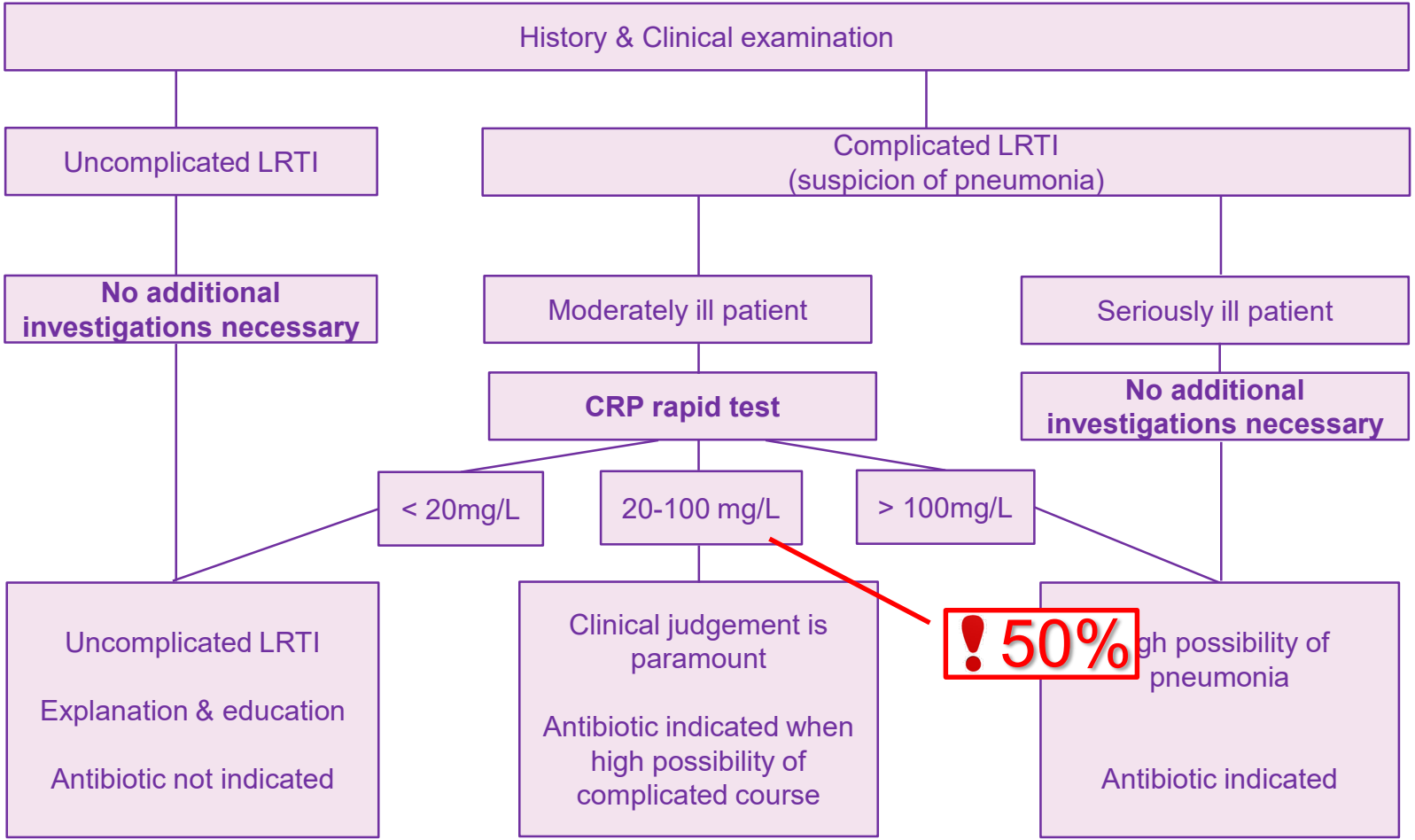


Use of C-reactive protein point-of-care tests as an adjunct to clinical examination likely reduces antibiotic use in primary care patients with acute (lower as well as upper) respiratory infections without affecting patient recovery rates or the duration of illness.

At present C-reactive protein is the only point-of-care biomarker available in primary care settings that may assist in guiding antibiotic prescribing for ARIs.

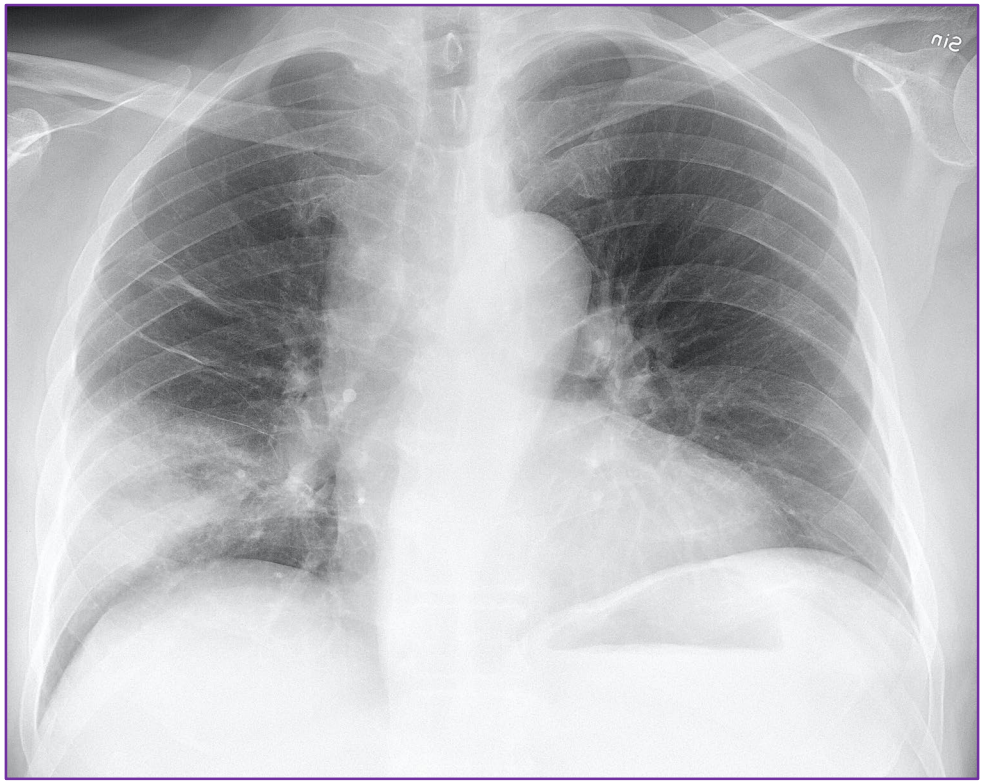
Aabenhus R et al. *Cochrane Database of Systematic Reviews* 2014; 11: CD010130


Point-of-care CRP
usual care
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
1.19.1 cluster randomised trials
Andreeva 2014 18 49 22 38 5.5% 0.63 [0.40, 1.00]
Cals 2009 20 65 31 59 5.8% 0.59 [0.38, 0.91]
Lemiengre 2014 117 455 106 381 11.5% 0.92 [0.74, 1.16]
Little 2013 304 920 407 844 15.5% 0.69 [0.61, 0.77]
Subtotal (95% CI) 1489 1322 38.2% 0.73 [0.60, 0.88]
Total events 459 566
Heterogeneity: Tau² = 0.02; Chi² = 6.62, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 3.21 (P = 0.001)
1.19.2 individually randomised trials
Cals 2010 56 129 73 129 10.6% 0.77 [0.60, 0.98]
Diederichsen 2008 179 414 184 398 14.1% 0.94 [0.80, 1.09]
Do 2016 441 1017 647 1019 16.4% 0.68 [0.63, 0.74]
Melbye 1995 54 108 68 131 10.6% 0.96 [0.75, 1.24]
Rebnord 2017 36 138 57 259 7.3% 1.19 [0.82, 1.70]
Van den Bruel 2016 10 26 9 28 2.7% 1.20 [0.58, 2.47]
Subtotal (95% CI) 1832 1964 61.8% 0.88 [0.73, 1.07]
Total events 776 1038
Heterogeneity: Tau² = 0.04; Chi² = 24.04, df = 5 (P = 0.0002); I² = 79%
Test for overall effect: Z = 1.28 (P = 0.20)
Total (95% CI) 3321 3286 100.0% 0.81 [0.71, 0.92]
Total events 1235 1604
Heterogeneity: Tau² = 0.02; Chi² = 31.82, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 3.21 (P = 0.001)
Test for subgroup differences: Chi² = 1.90, df = 1 (P = 0.17), I² = 47.5%
0.01
0.1
1
10
100
Favours Point-of-care CRP
Favours usual care



Verheij ThJM et al. *Huisarts Wet* 2011; 54(2): 68-92. **"NHG-standard acute cough"**

Chest X-ray: when and why?



Chest X-ray: when and why?

Clinical factors in the consideration to request a chest X-ray	Important (%)
Smoking	191 (85)
Duration of the complaints	186 (82)
Age	179 (79)
Presence of fever	98 (43)
Duration of fever	95 (42)
Response to previous antibiotics	92 (41)
Producing sputum, and sputum colour	28 (12)

Reasons to request a chest X-ray	Number of times indicated to be the most important (%[b])
Detection or exclusion of other lung abnormalities, such as a lung tumour	159 (69.7)
Confirm the diagnosis of pneumonia	87 (38.2)
Exclude the diagnosis of pneumonia	76 (33.3)
Reassuring the patient	22 (9.6)
Uncertainty about further policy	21 (9.2)
As a guide to decide on antibiotic … prescription	18 (7.9)



Groeneveld GH et al. *Eur J Gen Pract* 2019; 25(4): 229-235

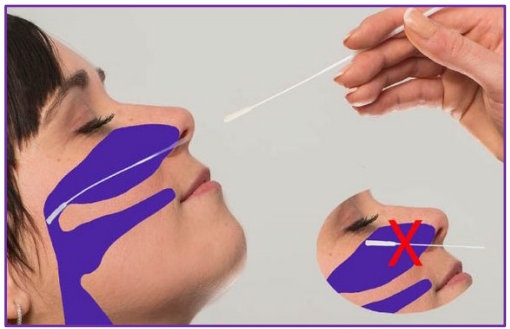
Other useful tests?



- Sputum microbiology? → **Gram/acid fast stain > culture**

- Serology for atypical pathogens? → **NO**
  - ✓ *Mycoplasma pneumoniae*
  - ✓ *Chlamydophila pneumoniae*

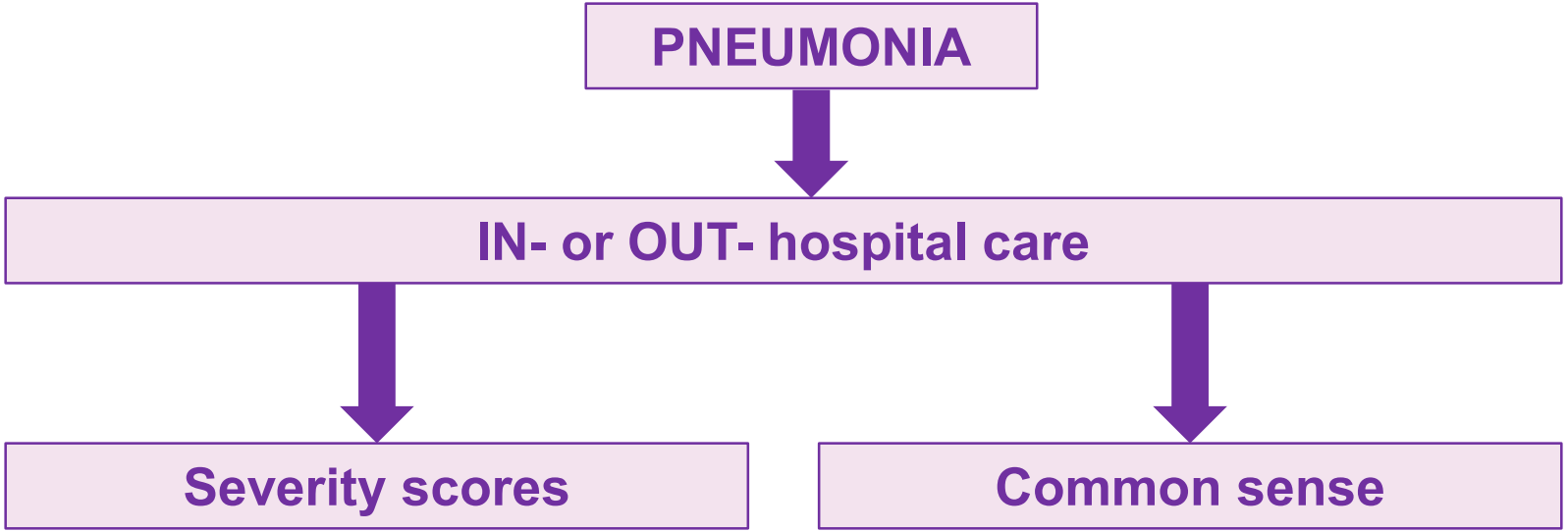
- Urinary antigen? → **NO**
  - ✓ *Legionella pneumophila* SG1
  - ✓ *Streptococcus pneumoniae*



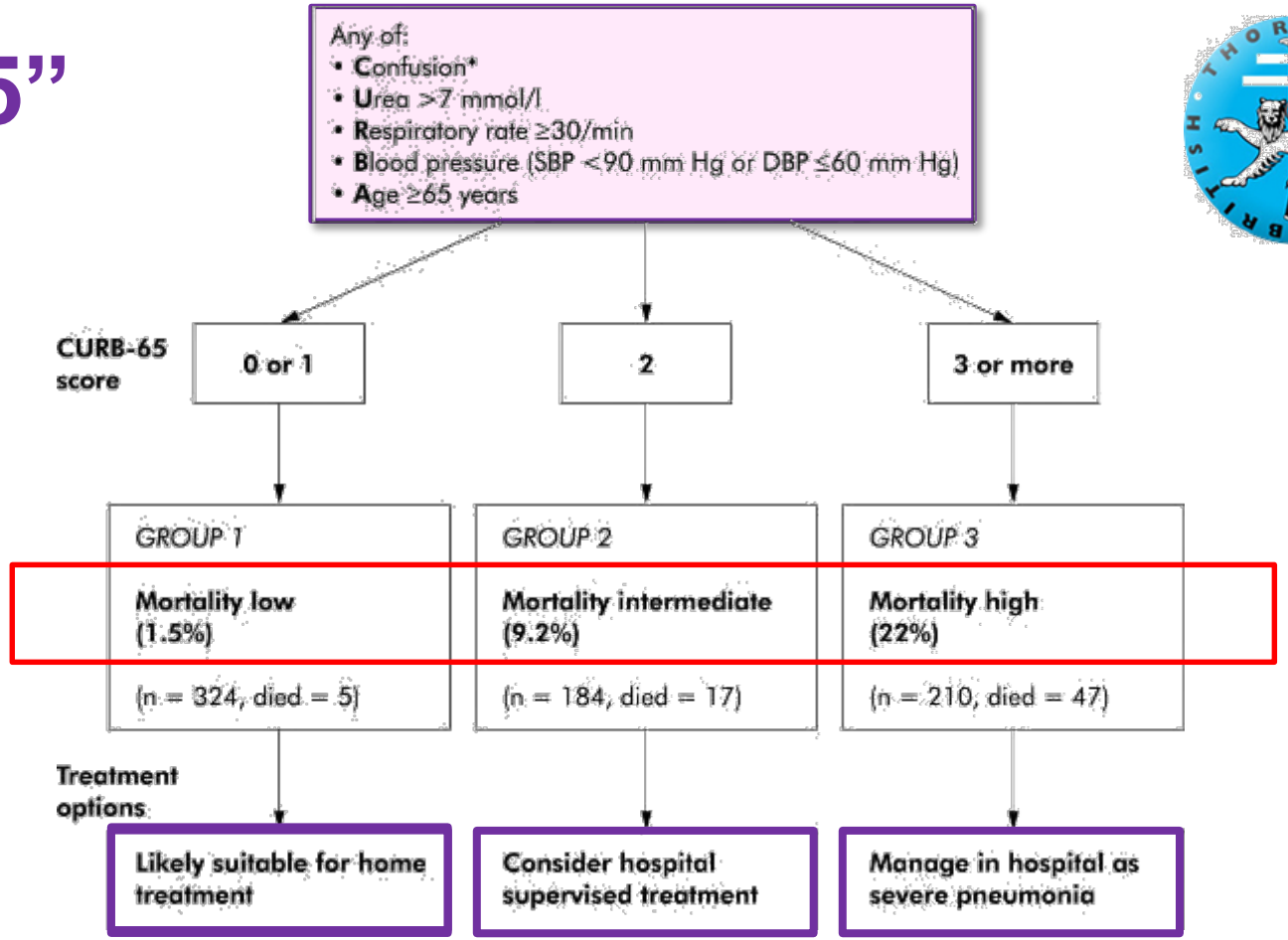
- PCR on nasopharyngeal swab? → **seasonal testing for influenza**

Metlay JP et al. *Am J Respir Crit Care Med* 2019; 200 (7), e45-e67

Pneumonia: severity assessment



"CRB-65" rule

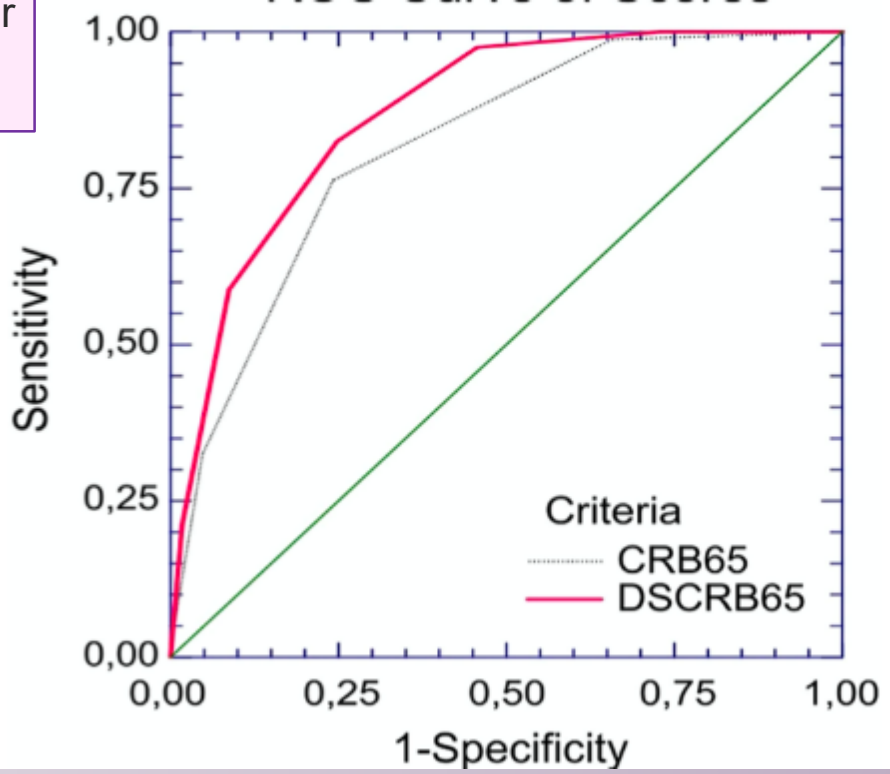


Lim WS et al. *Thorax* 2003; 58: 377-382

+ Underlying disease
- malignancy
- heart failure
- renal/liver diisease
- cerebrovascular disorder

+ SaO_2 <90%

Improvement of CRB-65 as a prognostic tool in adult patients with community-acquired pneumonia

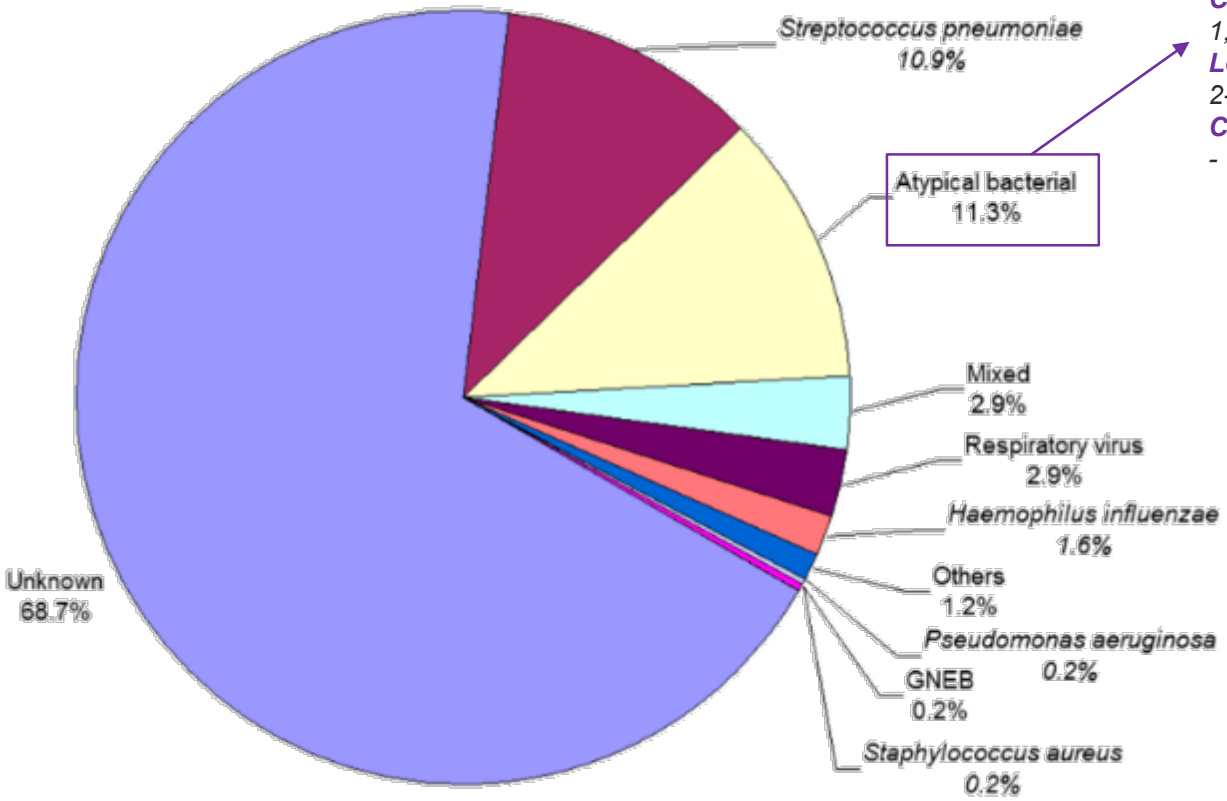


30d. mortality

	AUC
CRB-65	0.82
DS CRB-65	0.87

Dwyer R et al. *BMJ Open Research* 2014; 1: e000038

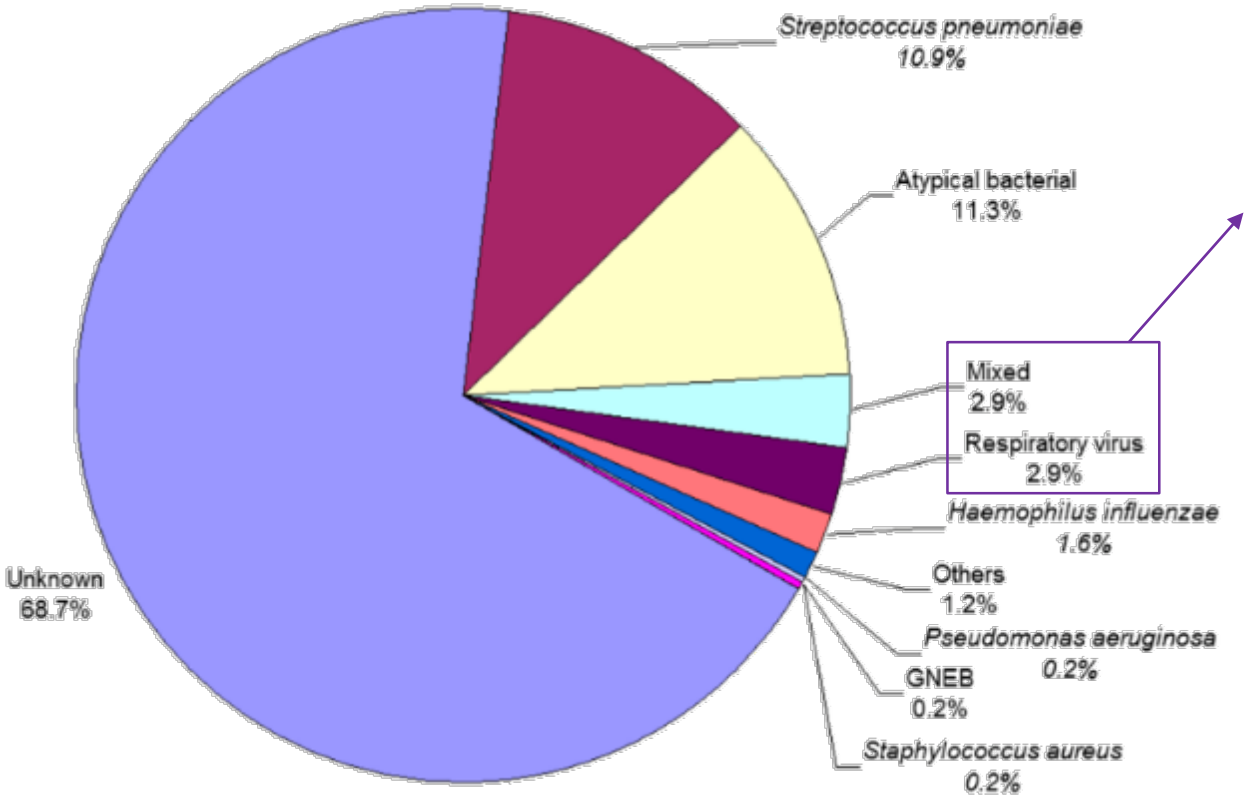
Etiology of CAP - outpatients



Mycoplasma pneumoniae
1,3 – 18%
Chlamydophila pneumoniae
1,8 – 5%
Legionella pneumoniae
2-6%
Coxiella burnetii
-

Cilloniz C et al. *Thorax* 2011; 66(4): 340-346 – Cilloniz C et al. *Intensive Care Med* 2016; 42: 1374-1386

Etiology of CAP - outpatients

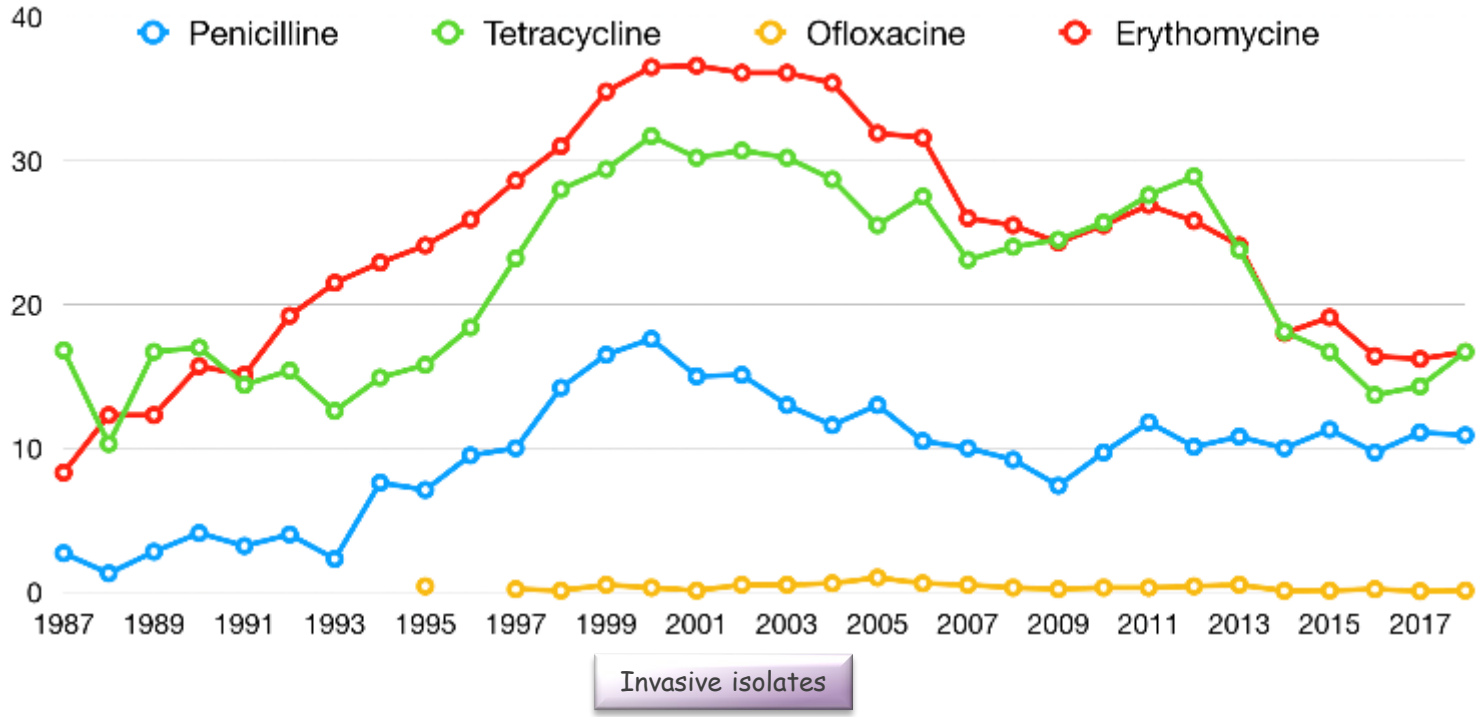


Viruses present in up to **25%** of pts with CAP

- **Influenzavirus**
- **Rhinovirus**
- **Coronavirus**
- **Para-influenzavirus**
- **RSV**
- **hMPV**
- **Adenovirus**

Burk M et al. *Eur Resp Rev* 2016; 25: 178-188 -- Alimi Y et al. *J Clin Virol* 2017; 95: 26-35

S. pneumoniae - resistance



Antibioticabeleid bij CAP

- CAP 1: no co-morbidities – younger age
  → start with **amoxycillin** 3 x 1000mg/d

- CAP 2: co-morbidities – older age
  → start with **amoxyclavulanate** 3 x 875mg/d (± amoxycillin)

- If no improvement after 2-3days
  → add therapy to cover atypicals
  > add macrolide (**azithromycin** 500mg/d or **clarithromycin** 2 x 500mg/d)
  > switch to **moxifloxacin** 400mg/d
- IgE-mediated hypersensitivity or severe intolerance
  → **moxifloxacin** 400mg/d

Duration of antibiotics treatment

- Mostly **5-7 days**
- Duration should be guided by a validated measure of clinical stability
- Bronchiectasis ⇨ 14 days
- Biomarkers as PCT of little use

Polverino E et al. *Eur Resp J* 2017; 50(3): 1700629 -- Tansarli GS et al. *Antimicrob Agents Chemother* 2019 Apr 25; 63(5)

Time to Clinical Stability in Patients Hospitalized With Community-Acquired Pneumonia

Implications for Practice Guidelines

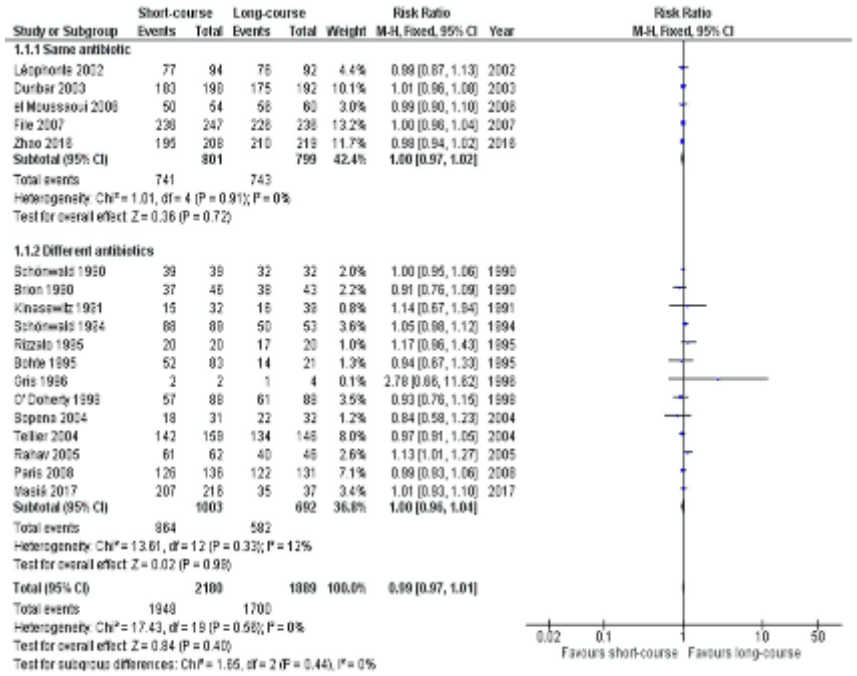
Ethan A. Halm, MD, MPH; Michael J. Fine, MD, MSc; Thomas J. Marrie, MD; Christopher M. Coley, MD; Wishwa N. Kapoor, MD, MPH; D. Scott Obrosky, MS; Daniel E. Singer, MD

Criterion for Stability	Unstable on Day 1, No. (%)	Time to Stability	
		Median, d	Interquartile Range, d
Systolic blood pressure ≥90 mm Hg†	50 (7)	2	2-3
Heart rate ≤100 beats/min†	385 (56)	2	2-3
Respiratory rate, breaths/min†			
≤24	337 (49)	3	2-4
≤22	489 (71)	3	2-6
≤20	537 (78)	4	3-7
Temperature, °C (°F)‡			
≤38.3 (101)	314 (46)	2	2-3
≤37.8 (100)	432 (63)	3	2-4
≤37.2 (99)	550 (80)	3	2-6
Oxygen saturation, %§			
≥90	142 (23)	3	2-6
≥92	188 (31)	3	2-6
≥94	237 (39)	4	2-8
Ability to eat†‖	73 (11)	2	2-8
Mental status¶	56 (8)	3	2-4

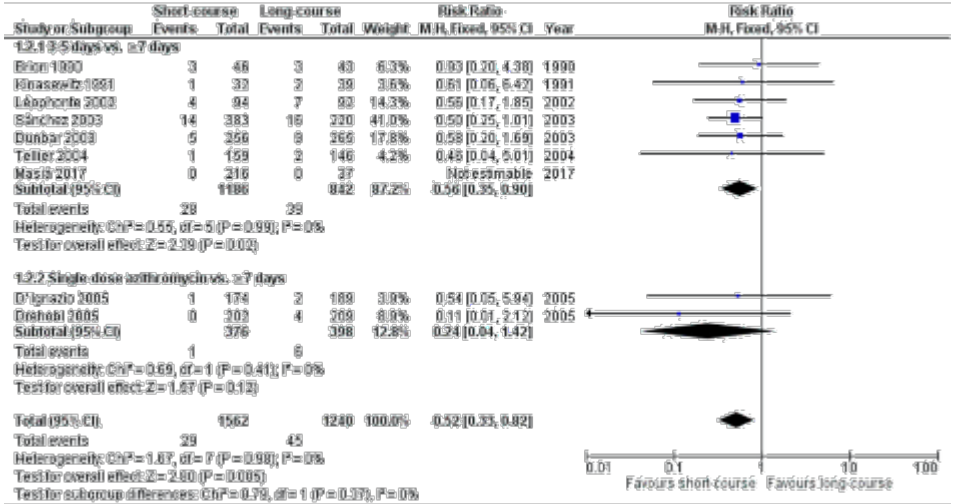
JAMA 1998; 279: 1452-1487

Systematic Review and Meta-analysis of the Efficacy of Short Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults

Clinical cure



Mortality



Tansarli GS et al. *Antimicriob Agents Chemother* 2018; 62 (9): e00635-18

Follow-up chest X-ray

- **Not recommended** in pts with CAP whose symptoms have resolved within 5 to 7 days

- Limited data about usefullness
- Most concern about lung malignancy not recognized at time of pneumonia (1-4%)

- Criteria for lung-cancer screening should apply

Little BP et al. AJR *Am J Roentgenol* 2014; 202: 54–59 -- Macdonald C et al. *Intern Med J* 2015; 45: 329–334

Casus: 78 jaar oud



- *Bekend met diabetes mellitus en arteriële hypertensie*
  Medicatie: Metformine, langwerkend insuline en hydrochloorthiazide

- *Hoest sinds vier weken, met geel sputum.*
  Afgelopen week drie dagen koorts gehad, nu niet meer
- *KO: geen dyspnee, O_2 sat 91%, longen wat verspreide rhonchi*

- *<u>Vraag</u>:*
  Verdere diagnostiek? Verder beleid?




THANK YOU FOR YOUR ATTENTION!
ANY QUESTIONS?